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MEMORANDUM January 23, 2001

SUBJECT: REVISED Oxadiazon Quantitative Risk Assessment (Q_1^*) Based On ICR-JCL Mouse and SPF Wistar Rat Dietary Studies With $^3/_4$'s Interspecies Scaling Factor

P.C. Code 109001

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Conclusion

The most potent unit risk, Q_1^*(mg/kg/day)$^{-1}$, of those calculated for Oxadiazon is that for male mouse liver adenoma and/or carcinoma combined tumor rates at 5.52 x 10^{-2} in human equivalents. The dose levels used from the 98-week dietary study were 0, 3, 10, 100, and 1000 ppm of Oxadiazon. The corresponding tumor rates were 3/51, 1/55, 4/57, 11/58, and 29/55, respectively.

Background

On September 3, 1986, the Toxicology Branch Peer Review Committee classified Oxadiazon as a Group B2 - probable human carcinogen, and recommended that, for the purpose of risk characterization, a low dose extrapolation model be applied to the experimental animal tumor data for quantification of human risk (Q_1^*). A Q1* based upon male liver (carcinoma and/or adenoma) tumor rates was generated using mg/kg b.w.^$^2/_3$'s/day cross species scaling factor (Oxadiazon hand-written memo, B. Fisher, 3/16/87).

This revised memo has been generated in response to new, more appropriate chronic/oncogenicity studies submitted to the Agency and to reflect the Agency policy change from use of the $^2/_3$'s to the $^3/_4$'s scaling factor in 1994[1]. Quantifications of risk have subsequently

[1]See memo - Deriving Q_1^*s Using the Unified Interspecies Scaling Factor, P.A. Fenner-Crisp, Director, HED, 7/1/94.

been estimated for these new studies. The most potent unit risk will be used for the purpose of lifetime cancer risk assessment by the Agency. In this case, the most potent unit risk, Q_1^*, is that for male mouse liver adenoma and/or carcinoma combined tumor rates at 5.52×10^{-2} in human equivalents.

All unit risks have been converted from animals to humans by use of the $^3/_4$'s scaling factor (Tox_Risk program, Version 3.5, K. Crump, 1994)[1]. For the conversion to human equivalents, weights of 0.03 kg for the mouse, 0.35 kg for the rat, 70 kg for humans, the use of 98 weeks for the mouse life-span default and 104 weeks for the rat life-span default were used.

It is to be noted that the Q_1^* $(mg/kg/day)^{-1}$ is an estimate of the upper bound on risk and that, as stated in the EPA Risk Assessment Guidelines, the true value of the risk is unknown, and may be as low as zero.

Dose-Response Analysis

There were no significant incremental changes in mortality with increasing doses of Oxadiazon in male or female mice or rats reported in the studies. The unit risks, Q_1^*'s, were obtained by the application of the Multi-Stage model (Tox_Risk program, Version 3.5, K. Crump, 1994).

Male mice had a significant increasing trend at $p < 0.01$, and significant differences in the pair-wise comparisons of the 100 ($p < 0.05$) and 1000 ($p < 0.01$) ppm dose groups with the controls, for liver adenomas and/or carcinomas combined.

Female mice had a significant increasing trend at $p < 0.01$, and a significant difference in the pair-wise comparison of the 1000 ppm dose group with the controls at $p < 0.05$, for liver adenomas and/or carcinomas combined. There was also a significant difference in the pair-wise comparison of the 1000 ppm dose group with the controls for malignant lymphomas at $p < 0.05$.

Male rats had a significant increasing trend at $p < 0.01$, and significant differences in the pair-wise comparisons of the 100 ($p < 0.05$) and 1000 ($p < 0.01$) ppm dose groups with the controls, for liver adenomas and/or carcinomas combined.

There were no significant trends or pair-wise comparisons for the liver tumors of female rats.

Additional Q_1^* Calculations

The unit risk, $Q_1^*(mg/kg/day)^{-1}$, of Oxadiazon based upon female mouse malignant lymphoma tumor rates is 2.89×10^{-2} in human equivalents. The dose levels used from the 98-week dietary study were 0, 3, 10, 100, and 1000 ppm of Oxadiazon. The corresponding tumor rates were 16/52, 25/53, 19/46, 21/48, and 27/51, respectively.

The unit risk, $Q_1^*(mg/kg/day)^{-1}$, of Oxadiazon based upon female mouse liver adenoma and/or carcinoma combined tumor rates is 1.31 x 10^{-2} in human equivalents. The dose levels used from the 98-week dietary study were 0, 3, 10, 100, and 1000 ppm of Oxadiazon. The corresponding tumor rates were 1/52, 0/53, 0/46, 1/48, and 7/51, respectively.

The unit risk, $Q_1^*(mg/kg/day)^{-1}$, of Oxadiazon based upon male rat liver adenoma and/or carcinoma combined tumor rates is 3.34 x 10^{-2} in human equivalents. The dose levels used from the 104-week dietary study were 0, 3, 10, 100, and 1000 ppm of Oxadiazon. The corresponding tumor rates were 0/53, 1/55, 1/54, 5/54, and 12/52, respectively.

The unit risk, $Q_1^*(mg/kg/day)^{-1}$, of Oxadiazon based upon female rat liver adenoma and/or carcinoma combined tumor rates is 8.16 x 10^{-3} in human equivalents. The dose levels used from the 104-week dietary study were 0, 3, 10, 100, and 1000 ppm of Oxadiazon. The corresponding tumor rates were 1/52, 1/52, 1/55, 1/53, and 3/55, respectively.

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